

Testosterone: Friend or foe for the cardiovascular system in men?

Testosterone: Friend or foe?

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Abstract
Epidemiological studies showed that cardiovascular diseases occur 7-10 years earlier in men than in women. One in two men and one in three women will have coronary artery disease events at the age of 40, and this observation is attributed to many factors, including differences in the steroidal hormonal status. In experimental trials, testosterone showed both beneficial and deleterious effects on the cardiovascular system. In addition, some trials found low levels of serum testosterone in men with coronary artery disease or heart failure and that patients with hypogonadism are at higher risk of cardiovascular diseases than patients with a normal serum level of testosterone. Clinical studies demonstrated cardiovascular deleterious effects of hypogonadism but no improvement with testosterone replacement therapy. It is unclear whether the differences in cardiovascular risk between men and women are due to the hormonal status or socio-cultural status.

Keywords
Testosterone; Hypogonadism; Inflammation; Cardiac hypertrophy; Coronary artery disease

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Introduction

Testosterone is synthesized in the Leydig cells in the testes and has a major contribution to the apparition of the masculine characters, starting in the intrauterine life. The effects of testosterone are more complex and involve many other body systems. The traditional opinion is that masculine steroid hormones are responsible for the lifelong higher cardiovascular risk profile in men than in women. However, patients with adipose-genital syndromes and low serum testosterone levels have more cardiovascular problems than men with normal serum testosterone levels. The cardiovascular effects of testosterone are controversial.

Testosterone synthesis and metabolism

The synthesis of testosterone begins in intrauterine life in XY chromosomes fetuses, in which the SRY genes on the Y chromosome induce the evolution of the undifferentiated gonad into testes through a cascade of gene activations, between the 7th and the 12th week of pregnancy [1]. Testosterone stimulates the development of epididymis, vas deferens, and seminal vesicles. Dihydrotestosterone (DHT), which is testosterone's more active derivate, stimulates the development of prostate and male external genitalia [1,2]. It has also anabolic effects on musculoskeletal development and brain influences [3].

After birth, synthesis of testosterone occurs almost exclusively in Leydig cells in the interstitial tissue of the testes by local de novo synthesis of cholesterol from acetyl coenzyme A, followed by the cleavage of a side chain from cholesterol by CYP11A1-cholesterol side-chain cleavage enzyme, which is bound to the inner membrane of the mitochondria in steroidogenetic but not in other tissues [4]. In extragonadal tissues such as liver, kidney, adipose tissue, there is also a small testosterone production from circulating weak adrenal androgen precursor, dehydroepiandrosterone (DHEA). Testosterone is enzymatically transformed by 5 α -reductase in dihydrotestosterone (DHT), which has 3-10 more molar potency than testosterone. Testosterone leaves the Leydig cells by passive transport and circulates in blood-free (1-2% form total testosterone) or bound to sex hormone-binding protein, androgen-binding protein, and albumin.

The metabolism of testosterone consists of transformation by 5- α reductase in DHT (5-10% of total testosterone), by aromatase in estradiol (0.2% of total testosterone), and in hepatic inactivation by oxidation and conjugation to glucuronides followed by biliary and urinary excretion of the inactive metabolites [5]. There are 3 types of 5- α reductase: one in brain, skin, liver, and kidney (5- α reductase type 1); the second in prostate, skin, and liver (5- α reductase type 2); the third in many tissues, without steroid activity, involved in fatty acid metabolism (5- α reductase type 3). The aromatase pathway is in the brain, bone, but not in the liver or muscle. The small local production of estradiol together with the effects of androgens on local androgen receptors are responsible for bone and brain androgen effects (Figure 1).

Testosterone reaches maximum serum level at approximately age 30 and after 40 years its level declines at a rate of 1% to 2% annually [6].

Luteinizing hormone (LH), which has a pulsatile pattern

production in the anterior pituitary gland, binds to a receptor on the Leydig cell membrane and stimulates the synthesis of testosterone from cholesterol. Follicle-stimulating hormone (FSH), which is also produced in the anterior pituitary gland, binds to FSH receptors on Sertoli cells in testes and stimulates germ cells to develop into mature sperm cells (spermatogenesis). The production of LH and FSH is stimulated by the hypothalamic gonadotropin-releasing hormone. Serum level of free testosterone and DHT controls the secretion of gonadotropin-releasing hormones by negative feedback mechanism [3, 4].

The effects of testosterone

The effects of testosterone are mediated by its' binding to the cytoplasmic androgen receptors encoded by a single gene located on the X chromosome [5]. They are chaperoned by heat shock proteins forming a complex that migrates into the cellular nucleus and activates genes linked to the androgen activity. The nuclear androgen receptors are ubiquitously expressed but with variable levels of expression and androgen sensitivity [5]. There is also a non-androgen receptor direct rapid membrane effect of testosterone on G-protein-coupled receptors and subsequent alterations in cytoplasmic calcium and potassium channel activity [7].

Cardiovascular and cardiometabolic effects of testosterone

Epidemiological data demonstrate that men are prone to develop cardiovascular diseases earlier than women, especially arterial hypertension and coronary artery disease [8-10]. At the same time, hypogonadism, irrespective of its cause, is associated with a greater risk of cardiovascular disorders, and men with ischemic heart disease or heart failure have a lower level of serum testosterone.

Svartberg J. et al. [11] demonstrated in 1264 men that arterial hypertension and cardiac hypertrophy evaluated by echocardiography are associated with a low testosterone level. However, this association is no longer found if the data are adjusted to the body mass index.

To complicate the interpretation of these findings, some of the effects of testosterone can be attributed in fact to the effects of estrogen produced from the testosterone by the aromatase pathway [11].

According to Melchert and Welder [12], there are four mechanisms related to the cardiovascular deleterious effects of testosterone: a direct myocardial injury, an atherogenic effect, a thrombogenic effect, and an increased propensity to vasospasm by promoting the inflammatory and endothelial dysfunction [13].

a)Cardiac hypertrophy. Androgen receptors are present in cardiac myocytes and are responsible for the cardiac deleterious effects of testosterone proved by experimental and clinical studies. In a study involving 12 adult male Wistar rats, those treated with high-dose testosterone had cardiac hypertrophy and high levels of caspase-3, which is an apoptosis marker suggesting a direct myocardial injury [13]. Testosterone stimulates cardiac hypertrophy via a direct androgen receptor-mediated pathway involving the overexpressed cGMP-specific phosphodiesterase 5 (PDE5). At the same time, estrogen can

initiate an autophagic cytoprotection of the myocardial cells by activating the estrogen receptors in the heart [3].

b) Cardiac fibrosis. Experimental data demonstrated that male mice have more cardiac fibrosis under pressure overload than female mice. Clinical data also demonstrated greater myocardial fibrosis and inflammation in men than in women in pressure-overload diseases associated with cardiac hypertrophy [3].

c) Androgens potentiate angiotensin II-induced renal vasoconstriction by Rho kinase-mediated Ca^{2+} sensitization, as demonstrated by an experimental study in New Zealand genetically hypertensive male rats [14]. Also, androgens up-regulate the renin-angiotensin system and directly increase the reabsorption of sodium in the proximal renal tube [15].

d) Men have a lower level of HDL cholesterol than women, but it is uncertain whether this is due to the high level of testosterone in men or high level of estrogen in women [8]. There are two genes involved in HDL catabolism which are up-regulated by testosterone: hepatic lipase and scavenger receptor B1 (SR-B1) [16]. Their activity leads to a decreased serum level of HDL cholesterol and also of total cholesterol [16].

Testosterone levels are negatively correlated to the serum levels of total cholesterol, LDL cholesterol, and triglycerides, but not all studies confirm these findings [16].

On the other hand, testosterone increases the expression of pro-atherogenic genes, atheroma plaque volume, coronary calcifications, adherence of white blood cells to the endothelial cells, and lipid loading of the macrophages [8,17].

e) Androgens influence also the inflammatory markers but data are controversial. Experimentally, dihydrotestosterone is associated with increased human monocyte adhesion to endothelial cells [18]. There is controversy regarding its effects on vascular cell adhesion molecules (VCAM) and C reactive protein (CRP) expression [17].

On the other hand, pro-inflammatory cytokine levels, such as IL-6, TNF- α , IL-1 β , IFN- γ , decrease, and anti-inflammatory cytokine IL-10 increases under the action of testosterone [17].

f) Carotid intima-media thickness is higher in men at andropause [19]. Mäkinen et al. [20] in Turku Aging Male Study, which involved 99 men at andropause, demonstrated a higher maximal intima-media thickness compared to controls in the common carotid (1.08 ± 0.34 vs. 1.00 ± 0.23 , $p < 0.05$) and in the carotid bulb, inversely correlated with serum testosterone level.

g) Endothelium-dependent brachial artery dilatory capacity is increased in androgen deprived men but reduced in women taking high doses of androgens [8].

h) Experimentally intracoronary administration of testosterone increases coronary blood flow in men with coronary heart disease [5, 8]. This effect seems to be independent of the endothelium; experimental studies have shown that testosterone does not influence endothelial nitric oxide activity. The mechanism involved in coronary vasodilatation induced by testosterone is the modulation of vascular smooth muscle cell membrane K and Ca ion channels [5]. Tharp et al. [21] experimentally demonstrated in male Yucatan miniature swine that endogenous testosterone limits coronary neointima formation after coronary percutaneous dilatation, but there is no such information about humans.

i) Regarding the blood coagulation, testosterone experimentally increases human platelet thromboxane A2 receptor density and aggregation [22]. According to the Copenhagen City Heart Study, which followed 4673 men for 21 years between 1981-1983, there is no association between the level of serum testosterone and the risk of thrombotic events [7, 23], despite previous reports. The thrombotic activity of testosterone reported in other studies, was attributed to its conversion to estradiol by aromatase and increased blood viscosity because of enhanced erythropoietin synthesis by testosterone [23]. Moreover, the physiological blood concentration of testosterone protects from thrombotic events [23]. Jin H et al. [24] demonstrated on human umbilical vein endothelial cells that the physiological level of testosterone enhances the anticoagulant activity by stimulation of tissue factor pathway inhibitor (TFPI) and tissue plasminogen activator (tPA) expression and inhibition of plasminogen activator inhibitor-1 (PAI-1) secretion by the endothelium.

j) Testosterone shortens the QTc interval on ECG and protects from severe ventricular tachycardia. In vitro, androgens lead to the shortening of ventricular action potential duration. The mechanism seems to be the decrease in the myocardial cells L-type calcium channel current and an increase of several K currents, such as rapidly activating delayed rectifier current (I_{Kr}), slowly activating delayed rectifier current (I_{Ks}), and inward rectifier current (I_{K1}) [25-27]. After orchiectomy, the QT interval becomes longer than in healthy age-matched male subjects.

Findings from clinical data on cardiovascular risk in hypogonadal men

Clinical studies demonstrated that low testosterone level correlates with increased risk of cardiovascular morbidity and mortality in men. Serum testosterone is decreased in chronic conditions such as type 2 diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary diseases, obesity, and infection with human immunodeficiency virus [5]. Hypogonadal men have a greater cardiovascular risk profile while normal testosterone levels may offer protection against the development of atherosclerosis in middle-aged men [5]. Testosterone increases the angina threshold in men with coronary artery disease by producing coronary vasodilation [28, 29]. According to 6 studies including 774 patients until 2010, men with coronary artery disease have low levels of serum testosterone. Nevertheless, each of these studies included a small number of patients, and study design and endpoints were inhomogeneous [5, 30]. Li L et al. [31] demonstrated in 803 patients an inverse correlation between serum testosterone and the severity of coronary artery disease. However, 4 studies involving 3593 patients with coronary artery disease did not demonstrate a relationship with the serum level of testosterone [5, 32]. Again, each of these studies had limitations, related to the small sample size, lack of cardiac catheterization, suboptimal methods used for measurement of serum testosterone [5]. Men with heart failure have a lower level of serum testosterone related to poor prognosis [5]. Some studies demonstrated that low testosterone/estradiol ratio in hypogonadal men is a risk factor for vascular inflammation and subsequent cardiovascular events [33].

Table 1. Cardiovascular effects of testosterone

	Positive effects	Deleterious effects	Controversy
Cardiac effects [13,14,15]	Coronary vasodilation	Cardiac hypertrophy Cardiac fibrosis Increased angiotensin II vasoconstriction	
	QTc shortening on ECG		
Inflammatory status [12,29]	Increased IL-10	increased human monocyte adhesion to endothelial cells	
	Pro-apoptotic effects	increased white blood cell adherence to endothelium	
	Decreased CRP, IL-6, TNF-α, IL-1 β, IFN-γ VCAM-1	Increased VCAM-1 and CRP	Effects on VCAM and CRP expression
	Stimulated TFPI and tPA expression	Increased TxA2, human platelets receptor density and aggregation	Clinical controversial effects Some studies demonstrated that the physiological blood concentration of testosterone protects from thrombotic events
Coagulation status [23, 24]	Inhibition of PAI-1 secretion by the endothelium.		
Carotid intima-media thickness [20]	Decreased intima-media thickness		
Vascular tone [8, 12]		Increased aortic vasoconstriction Attenuation of the vasodilator effect of adenosine	Endothelium-dependent brachial artery dilatory capacity is increased in androgen deprived men, but reduced in women taking high doses of androgens
Atherogenesis [16, 17]		Increased expression of pro-atherogenic genes Increased coronary calcification Increased lipid loading of macrophages Increased atherosclerotic plaques	
Cholesterol and triglycerides serum level [8, 16]	Decreased total cholesterol Decreased LDL cholesterol Decreased triglycerides	Decreased HDL cholesterol	Effects on LDL cholesterol, triglycerides
LDL cholesterol Total cholesterol [8]			Controversial data
Metabolic syndrome [16]	Decreased fat mass Increased lean mass Improved fasting glucose level		

CRP = C reactive protein; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α , IL-1 β = interleukin 1 β , IFN-γ = interferon γ; VCAM-1 = vascular cell adhesion molecule 1; IL-10 = interleukin 10; QTc = corrected Q-T interval on electrocardiogram; TFPI = tissue factor pathway inhibitor; tPA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor 1; LDL cholesterol = low density cholesterol; HDL cholesterol = high density cholesterol

There are also controversies regarding the relationship between the serum level of testosterone and cardiovascular mortality in clinical studies. However, 8 studies involving 10,838 patients demonstrate that cardiovascular mortality is greater in men with low serum testosterone levels [5].

There is a dual relation between the serum level of testosterone and the occurrence of type 2 diabetes mellitus. Men with type 2 diabetes mellitus had a lower level of serum testosterone, and

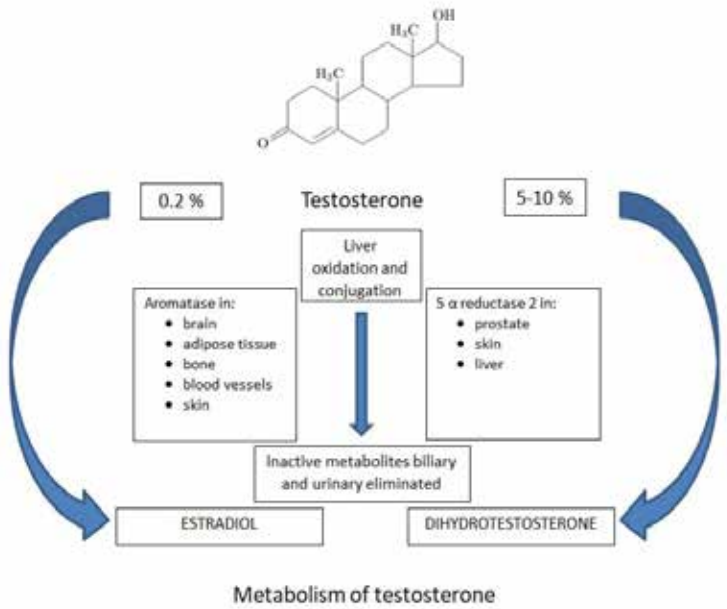


Figure 1. Testosterone metabolism; 5-10% of testosterone is transformed in dihydrotestosterone, the most active form, 0.2% is transformed in estradiol and the rest is inactivated in liver and biliary and urinary excreted.

also hypogonadism is a risk factor for the occurrence of type 2 diabetes mellitus [5, 19]. Testosterone replacement therapy improves glycosylated hemoglobin levels [34]. Better control of diabetes can be due to the decrease of metabolically active visceral adipose tissue by testosterone [35]. Hypogonadism is associated with increased body mass index, metabolic syndrome, and obesity, but the effects of testosterone on cholesterol and its subfractions are confusing.

Findings from testosterone replacement therapy trials

There are confusing data also about the effects of testosterone replacement therapy on cardiovascular pathology. Meta-analysis performed by Haddad RM et al. [36], Calof OM et al. [37], Fernandez-Balsells MM et al. [38] did not find differences regarding the cardiovascular events in men with hypogonadism who received or not testosterone replacement therapy. Patients with hypogonadism that received testosterone replacement therapy had higher hematocrit and lower HDL cholesterol serum levels than patients without therapy, but the clinical significance of these data was unclear [38]. Testosterone in Older Men with Mobility Limitations (TOM) trial demonstrated that patients over 65 years old with hypogonadism receiving testosterone replacement therapy can develop acute coronary syndromes, stroke, atrial fibrillation, elevated blood pressure, and peripheral edema more frequently than those without treatment. This study was prematurely stopped because of safety concerns [12, 39]. Other studies demonstrated that in men younger than 65 years with hypogonadism, who receive testosterone replacement therapy, the risk of cardiovascular adverse events was significantly increased if they had preexisting cardiovascular comorbidities [12, 40].

Differences in cardiovascular pathology between men and women

The differences in cardiovascular pathology between men and women were traditionally assigned to hormonal status. Women live longer than men and in the adulthood have a greater level of HDL cholesterol, lesser prevalence of arterial hypertension, later start of coronary artery disease, more frequent microvascular coronary artery disease, lesser cardiac fibrosis, myocardial infarction with normal coronary arteries, Takotsubo syndrome, heart failure with preserved or intermediate left ventricular ejection fraction. Meanwhile, the prognosis of the acute coronary syndrome is worse in women than in men. Are these gender differences related to biological aspects or socio-cultural factors? There is no simple answer to this question, despite many studies in this field because of a complex interplay between sex hormones, gender, socio-cultural environment, and other factors.

In conclusion, is testosterone friend or foe for the cardiovascular system in men?

Returning to the question of whether testosterone is a friend or a foe for the cardiovascular system in men, the answer is not simple. Traditional data demonstrate that adult men have greater cardiovascular risk than adult women. Testosterone is involved in cardiac hypertrophy, cardiac fibrosis, renal vasoconstriction, low HDL serum cholesterol level. On the other hand, the normal serum level of testosterone is a friend of the cardiovascular system of adult men, being associated with lesser carotid intima-media thickness and protecting from severe ventricular arrhythmias by favorably influencing the cardiac repolarization parameters. Endothelium-dependent brachial artery dilatation capacity is decreased by testosterone, but experiments with intracoronary administration of testosterone increase coronary blood flow in men with coronary heart disease. It has controversial effects on the other lipid subfractions and also on the vascular inflammatory and coagulation parameters (Table 1). Hypogonadism is a risk factor for cardiovascular disease, but testosterone replacement therapy does not improve patients' outcomes. These discrepancies can reflect the complexity of the problem and also the difficulty of performing experimental and clinically accurate studies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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